

CLAIMS:

1. A method of detecting an interaction between a bait polypeptide and a prey polypeptide comprising:

5 introducing a first nucleic acid encoding a first hybrid protein into a host cell, the first nucleic acid having a first exogenously activatable promoter, and the first hybrid protein having a DNA binding region and the bait polypeptide;

10 introducing a second nucleic acid encoding a second hybrid protein into the host cell, the second nucleic acid having a second exogenously activatable promoter different from the first exogenously activatable promoter, and the second hybrid protein having a transcriptional activation  
15 region and the prey polypeptide;

activating the first and second promoters using first and second exogenous activators to induce expression of the first and second hybrid proteins; and

20 detecting an interaction between the bait polypeptide and the prey polypeptide by activation of a detectable reporter gene in the host cell, wherein the DNA binding region binds near the reporter gene and the transcriptional activation region activates transcription of the reporter gene when brought into proximity to the reporter gene by an  
25 interaction between the bait polypeptide and the prey polypeptide;

wherein sensitivity of detecting an interaction may be continuously adjusted by altering the relative or absolute amount of at least one of the first or second hybrid  
30 proteins in the host cell and wherein amounts of the first and second hybrid proteins in the host cell are independent of one another.

2. The method of Claim 1, further comprising  
continuously adjusting the amount of the first hybrid  
protein in the host cell through activation of the first  
5 exogenous promoter.

3. The method of Claim 1, further comprising  
continuously adjusting the amount of the second hybrid  
protein in the host cell through activation of the second  
10 exogenous promoter.

4. The method of Claim 1, wherein the first nucleic  
acid further comprises a plurality of exogenous promoters  
operable to induce expression of the first hybrid protein in  
15 the host cell over a wider continuous range of amounts than  
the range obtainable using only one of the plurality of  
exogenous promoters.

5. The method of Claim 1, wherein the second nucleic  
20 acid further comprises a plurality of exogenous promoters  
operable to induce expression of the second hybrid protein  
in the host cell over a wider continuous range of amounts  
than the range obtainable using only one of the plurality of  
exogenous promoters.

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6. The method of Claim 1, further comprising  
detecting a detectable reporter protein produced by  
activation of the detectable reporter gene.

30 7. The method of Claim 1, wherein sensitivity of  
detecting an interaction may be continuously adjusted on a  
dose-responsive basis.

8. The method of Claim 1, further comprising  
interfering with activation of at least one of the first or  
second exogenously activatable promoters by providing a  
5 modulatory agent to the host cell.

9. The method of Claim 1, wherein at least one of the  
first or second exogenous activators comprises a natural or  
synthetic, metabolically active or inactive steroid, steroid  
10 analogue or steroid mimic.

10. The method of Claim 1, further comprising at least  
one of the first or second exogenous activators selected  
from the group consisting of: cortisol, cortisone,  
15 hydrocortisone, mineralcorticoids and mineralcorticoid  
analogues, dexamethasone estrogen, estradiol, estrone,  
progesterone, androgens, ecdysone, retinoid, steroids  
complementary to orphan receptors, other agent operable to  
interact with steroid responsive elements, and any  
20 combinations thereof.

11. The method of Claim 1, wherein at least one of the  
first or second exogenous activators comprises a membrane-  
active agent or analog thereof selected from the group  
25 consisting of: ionophores, anesthetic agents, detergents,  
amphoteric agents, hydrophobic agents, lipid-active agents,  
solvents, transmembrane signaling agents, intramembrane  
signaling agents, farnesylating agents, and any combinations  
thereof.

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12. The method of Claim 1, wherein at least one of the  
first or second exogenous activators comprises a small

molecular pharmaceutical agent selected from the group  
consisting of: antimicrobial agents, anti-tumor agents,  
nucleic acid-binding agents, cytoskeletal active agents,  
chelators, inducers, co-repressors, agents affecting  
5 intracellular trafficking, localization, protection and  
degradation of exogenous or endogenous mediators, hormones,  
and any combinations thereof.

13. The method of Claim 1, wherein at least one of the  
10 first or second exogenous activators comprises a biomolecule  
or natural or synthetic biopharmaceutical selected from the  
group consisting of: growth factors, cytokines, hormones,  
their cellular receptors, fragments thereof, mimics thereof,  
and any combination thereof.

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14. A method of detecting an interaction between a bait polypeptide and a prey polypeptide comprising:

introducing a first nucleic acid encoding a first hybrid protein into a host cell, the first nucleic acid  
5 having an estrogen-sensitive promoter, and the first hybrid protein having a GAL4 binding domain and the bait polypeptide;

introducing a second nucleic acid encoding a second hybrid protein into the host cell, the second nucleic acid  
10 having a glucocorticoid-sensitive promoter, and the second hybrid protein having a GAL4 transcriptional activation domain and the prey polypeptide;

activating the promoters to induce expression of the first and second hybrid proteins; and

15 detecting an interaction between the bait polypeptide and the prey polypeptide by activation of a UAS<sub>g</sub>-LacZ reporter gene in the host cell;

wherein sensitivity of detecting an interaction may be continuously adjusted by altering the relative or absolute  
20 amount of at least one of the first or second hybrid proteins in the host cell and wherein amounts of the first and second hybrid proteins in the host cell are independent of one another.

25 15. The method of Claim 14, wherein activating the promoters further comprises supplying estrogen or an estrogen analogue and a glucocorticoid or a glucocorticoid analog to the host cell.

30 16. The method of Claim 14, wherein sensitivity of detecting an interaction may be continuously adjusted by

altering the amount of estrogen or an estrogen analogue  
supplied to the host cell.

17. The method of Claim 14, wherein sensitivity of  
5 detecting an interaction may be continuously adjusted by  
altering the amount of glucocorticoid or a glucocorticoid  
analogue supplied to the host cell.

10 18. The method of Claim 14, further comprising  
continuously adjusting the amount of the first hybrid  
protein in the host cell through activation of the estrogen-  
sensitive promoter.

15 19. The method of Claim 14, further comprising  
continuously adjusting the amount of the second hybrid  
protein in the host cell through activation of the  
glucocorticoid-sensitive promoter.

20 20. The method of Claim 14, further comprising  
detecting LacZ produced by activation of UAS<sub>g</sub>-LacZ reporter  
gene.

25 21. The method of Claim 20, further comprising  
detecting LacZ using colorimetric analysis.